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HISTORICAL FUND
of the
NAVY MEDICAL DEPARTMENT

A committee has been formed with representation from the Medical Corps, Dental Corps, Medical Service Corps, Nurse Corps, and Hospital Corps for the purpose of creating a fund to be used for the collection and maintenance of items of historical interest to the Medical Department. Such items will include, but will not be limited to, portraits, memorials, etc., designed to perpetuate the memory of distinguished members of the Navy Medical Department. These memorials will be displayed in the Bureau of Medicine and Surgery and at the National Naval Medical Center. Medical Department officers, active and inactive, are invited to make small contributions to the fund. It is emphasized that all donations must be on a strictly voluntary basis. Funds received will be deposited in a Washington, D. C. bank to the credit of the Navy Medical Department Historical Fund, and will be expended only as approved by the Committee or its successor and for the objectives stated.

It is anticipated that an historical committee will be organized at each of our medical activities. If you desire to contribute please do so through your local historical committee or send your check direct, payable to Navy Medical Department Historical Fund, and mail to:

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Mass Prophylaxis of Epidemic Streptococcal Infections Experience at a Naval Training Center - Winter 1956-57

The most recent of the Navy Medical Department's continuing studies on practical and effective methods of controlling epidemic streptococcal infections in recruit populations is reported. The method of prophylactic intramuscular injection of benzathine penicillin G for this purpose was a direct outgrowth of the studies done at the same station in a previous winter by Schreier, et al.

Starting in December, when the prevalence of streptococcal infections began to increase, Schreier and his co-workers administered 600,000 units of benzathine penicillin G to all new recruits within a few days after their arrival at the station. Experience had shown that during most epidemics a large percentage of streptococcal infections were acquired in the first month of the training period. Administration of benzathine penicillin at the beginning of training theoretically offered almost complete protection for the first half of the training period.

In the current study, it was decided to employ the same dose of benzathine penicillin, but to administer it during the fourth instead of the first week of training. By this change, it was hoped that adequate therapy could be provided for such infections as had occurred before the injection and that protection from new infection would be provided between the fourth and eighth weeks of the 10-week period of training. In this way, only in the last 2 weeks would a recruit lack some protection against development of rheumatic fever if epidemic streptococcal infections occurred during the winter. It was further decided to administer a larger dose of benzathine penicillin G to a part of the population because the longer period of protection supposedly afforded by 1,200,000 units would further reduce the unprotected period at the end of training and comparative data were desired on the duration of protection.

The program of streptococcal prophylaxis was carried out on the male recruit population at the United States Naval Training Center, Bainbridge, Md., from October 29, 1956 to May 9, 1957.

A Navy recruit receives approximately 70 days of training. The first week consists mainly of processing and indoctrination during which recruits are grouped into companies of 96 men. The company remains nearly intact during the remaining 9 weeks of scheduled training which includes classroom work, physical conditioning, and military drill. Men in the company share a large dormitory, attend classes and meals together, and are otherwise in close contact with each other throughout training. A small number of men are set back into another company as a result of academic failure, illness, or disciplinary action. These men are often on the station for much longer than 70 days.

During the study, all new recruits except those who reported a definite history of previous reaction to penicillin were given an injection of benzathine penicillin during the fourth week of training, approximately 22 to 28 days after arrival at the station. A total of 12,858 men received an injection and 237 (1.8%) were excused because of a history of allergy to penicillin. Men in each company not giving a history of reaction to penicillin were divided into two groups by the last digit of the service number. Those with even numbers were given 600,000 units of benzathine penicillin intramuscularly, and those with odd numbers were given 1,200,000 units.

The incidence of streptococaal disease and, more particularly rheumatic fever, during the winter of 1956-57 was the lowest in the history of this station which had a longstanding reputation for its annual epidemics.

The exact role that the prophylactic program played in this low incidence is difficult to define. In a mass prophylactic program designed to protect the entire population, controls are impossible. If any large group had been left untreated and incurred a considerable amount of streptococcal disease, the degree of stress to which the treated population would have been subjected would have been increased. As a result, more infections "breaking through" penicillin protection might occur among the treated group and give an erroneous impression of what could be achieved by a given dose of penicillin under conditions of lesser stress. On the other hand, a small control group of untreated recruits would probably have had less streptococcal disease than might normally have occurred because the majority of the population were protected and the degree of exposure or stress markedly reduced. When the control group influences the treated group, or the treated group the control in this fashion, a controlled study is obviously impracticable.

Because controlled studies cannot be carried out, the evaluation of a mass prophylactic program of the type employed must depend on repeated experience over a number of years, even though the experience in one winter is not strictly comparable to that of another winter. Some idea of the value of the current program can be gained by comparison with past experience in recruits at the same station. The results of the program employed by Schreier, et al. in the previous winter were thought to have been good, and the 27 cases of rheumatic fever that occurred were the lowest total for any winter in the past. When compared with that record, however, the occurrence of only 3 cases of rheumatic fever in the current winter constituted a remarkable record. The difference is far in excess of anything that might be attributed to the decrease in population at risk during the current study (20,000 including recruits on the station at the beginning and end of the study who were not treated) when compared to that at risk in the former study (30,000).

In comparison with the previous year, it appears that delaying the prophylactic injection had the effect of doubling the protection afforded by

a single injection. Undoubtedly, 4 weeks' delay would have been too long if there had been more streptococcal disease in the population at the beginning of the program. In that instance, more infections would probably have occurred in the first 2 weeks of training, and eradication of the organism after the longer interval might well not have prevented rheumatic fever from occuring.

Complete definition of the degree and duration of protection afforded by the two doses is not a simple problem. Preparations that appear to have about equal capabilities under conditions of stress prevailing when streptococcal infections are spreading slowly and sporadically may vary widely when the conditions of stress are those prevailing during an epidemic. The comparison in this study is, therefore, applicable only where the degree of stress is not very marked.

Infections broke through penicillin protection with equal frequency and at about the same intervals after injection of the two dosages of benzathine penicillin used. If—as has been commonly believed—the larger dose provides more complete and longer protection against streptococcal infection, it was not evident under the conditions of study. The data of Davis, et al. on the use of 900,000 units prophylactically are very similar to those obtained in this study if the populations at risk and degree of exposure to untreated populations are taken into account. These data further affirm the impression that a larger dose of benzathine penicillin does not necessarily increase the degree of protection afforded within the first 30 days after injection and cast some doubt on the validity of data considered by the American Heart Association in increasing the recommended dosage for patients receiving continuous prophylaxis against recurrent rheumatic fever from 600,000 units monthly to 1,200,000 units.

Numerous prophylactic studies of the past have indicated clearly that streptococcal infections and rheumatic fever could be completely prevented if enough penicillin is used at sufficiently frequent intervals. From a practical standpoint, however, the stopping place seems to be the point at which the medical problems created by reactions to penicillin begin to exceed the problems caused by streptococcal infections and their complications or sequelae. Under the present conditions of training Navy recruits at this station, it appears that the method of prophylaxis employed in the current study has afforded the maximum reduction in streptococcal infections that it will prove practicable to seek. Although reactions to penicillin were not a particular problem, any increase in the amount of penicillin might well create the condition under which reactions are more frequent than streptococcal infections. (McFarland, R. B., M. D., Captain Colvin, V. G., MC USN, Captain John R. Seal MC USN, Mass Prophylaxis of Epidemic Streptococcal Infections with Benzathine Penicillin G: New England J. Med., 258: 1277-1283 June 26, 1958)

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The Syndrome of Mineralocortocoid Excess

The effect of acute potassium deficiency on neuromuscular transmission and cardiac action is readily recognized and can be promptly repaired by administration of potassium salts. The consequences of longstanding potassium depletion—including both functional and anatomical changes in kidneys, heart, and muscle—are not so generally appreciated. Chronic depletion of potassium follows prolonged inability to ingest and absorb dietary potassium or loss through persistent diarrhea or abuse of laxatives. Potassium may be lost in urine because of disease involving the renal tubules or during dehydration, acidosis, or other disorders which impair normal renal conservation of potassium. Excessive "mineralocorticoid" action, due to increased secretion by the adrenal cortex or to exogenous corticosteroids, leads to potassium depletion with specific features which distinguish it from other forms of potassium loss.

When large doses of a typical mineralocorticoid, desoxycorticosterone, are given to patients without adrenals, sodium and water excretion are reduced, weight rises as extracellular fluid is accumulated; if overdosage is continued, edema increases to anasarca with signs resembling congestive cardiac failure. In normal man, however, large doses of desoxycorticosterone are followed by only minor increases in body weight. At first, sodium is retained, but after several days, normal sodium excretion is resumed despite continued administration of hormone. A normal secretion of the adrenal cortex is one requirement for the circulatory or renal readjustments which prevent undue accumulation of extracellular fluid. Although this homeostatic mechanism limits the increase in extracellular sodium, desoxycorticosterone induces continuous potassium loss in urine and, to a lesser extent, in feces so long as the diet contains ample sodium. Ammonium excretion in urine is increased without a fall in urine pH. If sodium intake is very low, these effects of mineralocorticoid excess on electrolyte balance are minimized or abolished.

These initial signs of mineralocorticoid excess are soon followed by further evidences of potassium depletion. There is increasing thirst and large volumes of dilute urine appear. Renal concentrating power is impaired, although urine flow can still be reduced by water deprivation or injection of vasopressin. Lassitude, muscular weakness, paralysis, and disturbances of cardiac action may follow, especially if sodium chloride is added to the diet. Plasma sodium and bicarbonate are increased while potassium and chloride concentrations are abnormally low.

Arterial hypertension appears in some patients after administration of corticosteroids. Other forms of potassium deficiency are generally associated with a fall in blood pressure, sometimes with vascular collapse. Arterial pressure is more readily increased in animals with reduced functioning kidney substance.

An excess of cortisol (hydrocortisone) induces a variable group of symptoms and signs often designated "Cushing's syndrome." The appearance of hypertension, edema, polyuria, weakness, and hypokalemia with hypochloremic alkalosis demonstrates the mineralocorticoid effects of cortisol which are usually accompanied by abnormal fat distribution, loss of muscle mass, weakness of connective tissue and blood vessels, altered organic metabolism, and other abnormalities. Most patients with adrenal cortical tumor show several signs of "Cushing's syndrome", but in certain instances, the hypertensive, renal, and electrolyte abnormalities are so prominent and the other signs so inapparent that the diagnosis of nephritis may be considered.

When aldosterone was discovered to be the most potent mineralocorticoid secreted by the adrenal cortex, the output of this new hormone was estimated in patients with hyperadrenocorticism due to tumor or hyperplasia. Some of these patients showed excess aldosterone excretion. Other patients whose output of aldosterone was within normal limits showed predominant evidences of mineralocorticoid effect and, in rare instances, no recognized signs of "Cushing's syndrome" despite significantly increased excretion of 17-hydroxycorticoids. Evidently, mineralocorticoid actions are not dependent solely on aldosterone, but may result from an excess of other adrenocortical hormones.

Adrenocortical carcinoma or bilateral hyperplasia commonly secretes an excess of several hormones which may appear as 17-ketosteroids, 17-ketogenic steroids, 17-hydroxycorticoids, and aldosterone in urine; and they may induce mixed biochemical and clinical patterns with elements of virilism, Cushing's syndrome, or mineralocorticoid excess.

Differential diagnosis of mineralocorticoid excess from other forms of hyperadrenocorticism may be difficult because various mixtures of hormones produce mixed syndromes which defy simple classification. Here, concern is not only with clinical and laboratory findings and with patterns of hormone secretion, but also with the histopathology which can be determined with certainty only by surgical exploration. There is also a curious mineralocorticoid-like syndrome associated with certain forms of carcinoma not arising in adrenal or pituitary glands.

As yet, it is too early to state what the ultimate minimum requirements for diagnosis will be. The minimum findings necessary for diagnosis in the past may be excessive when viewed in light of information available today. For the time being, the key finding will probably be arterial hypertension. This may be asymptomatic and may appear benign during the early stage.

Study of renal function may provide helpful information. Polyuria and polydipsia are important when present, but ordinary volumes of modestly concentrated urine may be excreted. Some limitation of concentrating power may be present and the normal action of pitressin in raising urine osmolarity

may fail even though there is some effect on urine flow. Neutral pH and low titratable acidity are regularly present, together with an unexpectedly high urine ammonia excretion in freshly voided urine. Bacteria growing in urine, or active pyelonephritis, could lead to an alkaline urine with high pH, low titratable acidity, and a high ammonia. Such a strongly alkaline urine would not be typical of mineralocorticoid excess in which the urine is more likely to be neutral. Urine cultures may be necessary to rule out an active urinary tract infection. Pyelonephritis and nephrosclerosis are possible late complications of mineralocorticoid excess.

Other evidence of mineralocorticoid excess is usually found in the form of reduced sodium concentration and increased potassium to sodium ratio in sweat, saliva, and stool.

If an adrenal tumor is visible in roentgenograms, including tomograms, pyelograms, or films taken after insufflation of oxygen in the presacral area, this information will facilitate surgery. The decision to operate should not rest on the roentgenologist because the tumor may be too small to demonstrate with certainty. Any patient who shows the definitive pattern of mineralocorticoid excess should be explored. An adenoma may be very small and elusive even when the adrenals are exposed. Removal of a tumor responsible for excessive secretion will result in cure, provided that secondary structural changes have not taken place. Early case finding and differential diagnosis are essential for the best result. (Luetscher, J. A. Jr., Editorial, The Syndrome of Mineralocorticoid Excess: Ann. Int. Med., 48: 1424-1431, June 1958)

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Osmotic Diuretic Treatment of Refractory Edema

Osmotic diuretics exert their action through physical rather than cellular metabolic effects. Osmotic diuretic action depends upon the presence of nonabsorbable particles within the isosmotic proximal tubule. These nonabsorbable particles cause retention of water within the proximal tubule to maintain a constant total osmolar concentration of 310 mOsM. per L. As compared with the preosmotic diuretic baseline, the water that is so retained progressively dilutes the sodium in the fluid as it traverses the proximal tubule Thus, an unchanged cell surface area containing the active metabolic sites for sodium resorption is exposed to a fluid of progressively lesser sodium concentration. The absorbing sites being less saturated, less sodium particles are absorbed (despite unaltered avidity of the individual cell sites), and more sodium particles are passed on distally. Within the proximal tubule, the additional nonabsorbed sodium and accompanying anions behave as osmotic diuretic particles and retain water that also is passed distally. In the distal convoluted tubule, absolute quantities absorbed, even

when maximal, are small fractions of the increased total quantities presented and explain the inability of the distal tubule to greatly modify the nature of the fluid presented to it. Urine during such marked osmotic diuresis is similar to the fluid leaving the proximal tubule in total concentration, pH, and individual ion concentrations. During such osmotic diuresis, the administration of a hypertonic solution (such as 1500 mOsM. per L.) coupled with excretion of urine with a 300 to 350 mOsM. per L. concentration indicates a net loss of solute.

Osmotic diuretics have been tried in refractory edema, both successes and failures having been reported. However, the sparsity of data and the infrequency of their use suggest that they have not been generally effective. From theoretical considerations, the limiting factor for their effectiveness is the presence of an adequate filtration rate to allow enough osmotic diuretic particles to reach the tubular lumen. Mercurial and osmotic diuretics potentiate each other's effects.

Mannitol, regarded as an almost inert nontoxic hexose, excreted by glomerular filtration alone, is an osmotic diuretic available for parenteral injection. The experience with mannitol administered intravenously with and without a mercurial diuretic in the treatment of refractory edema is the basis of this report.

Subjects were chosen who had marked edema of nephrosis, cardiac failure, or cirrhosis that was refractory to dietary salt restriction (less than 500 mg. of sodium per day) plus the usual diuretics, singly and in combination. In all patients, use of mercurial diuretics, aminophylline, ammonium chloride, and Diamox was unsuccessful.

Because of prolonged refractory edema, diuresis with mannitol administered intravenously was attempted. The dietary sodium content was constant for several weeks before, during, and after mannitol administration in all cases. Water intake was ad libitum. Patients were treated with infusions of 25% mannitol intravenously in amounts up to 2000 ml. (500 gm.) over periods of 4 to 8 hours. Usually a priming dose was followed by a slower infusion. Interruptions of the infusions occurred occasionally. A mercurial diuretic (Thiomerin) was given intravenously as single 2-ml. doses, or as 2 1-ml. doses 3 to 5 hours apart. These data demonstrate the effectiveness of an osmotic diuretic combined with a mercurial diuretic in treatment of refractory edema.

The increased effectiveness of the combination of an osmotic and a mercurial diruetic probably can be explained by their known different actions. Mannitol, by its water-retaining and sodium-diluting action, decreases the numbers of sodium-absorbing sites of the tubular cells that are exposed to sodium; Thiomerin reduces the avidity of each of these decreased numbers of sites for sodium resorption. The combined effects result in great proximal tubular rejection of sodium (and accompanying anions). Both mannitol and nonabsorbed sodium (due to mercurial effects on tubular cells) have

been shown to act as osmotic diuretics. The nonabsorbed ions and the mannitol retain water isosmotically in the proximal tubule and thus present excessive amounts of water and electrolytes to the distal tubule which are followed by excess excretion. It would be expected that any osmotic diuretic could be effectively combined with any metabolic diuretic that acted directly on the active cell mechanism for sodium transport. The factors influencing excretion of sodium are so numerous and variable that no absolute values of sodium excretion may be expected for given doses of mercurials, osmotic diuretics, or combinations of diuretics. What is demonstrated is the ability of osmotic diuretics to increase the tubular rejection of sodium from whatever level of rejection existed immediately prior to their use.

Despite the great losses of water, sodium, and chloride during the course of combined mannitol-Thiomerin treatment, no clinically significant changes of serum sodium, potassium, chloride, or bicarbonate concentrations occurred.

No substantial difference was found between the natriuretic or diuretic effects of mannitol plus Thiomerin in the patients with refractory edema of renal, cardiac, or hepatic origin. The diuretics were effective in shifting toward greater tubular rejection of sodium and water. The similarity of diuretic effects conforms with the concept that in these different states excessive sodium resorption by tubular cells due mainly to increased aldosterone effect is the final common pathway for the development of edema.

The clinical value of osmotic diuretics in refractory edema must be evaluated by more extended studies. The hazards of pulmonary edema in cardiac patients may be minimized by use of adequate doses of urea or other osmotic diuretics that are distributed throughout body water rather than extracellular fluid alone. In cirrhotic patients, the effects of repeated treatment gradually to remove extensive ascites and peripheral edema must be evaluated.

The use of (physical) osmotic diuretics in large adequate doses in combination with (metabolic) tubular cell sodium resorption blocking diuretics should be considered when edema states are refractory to all other diuretic therapy. (Bernstein, L. M., Blumberg, B., Arkin, M. C., Osmotic Diuretic Treatment of Refractory Edema: Circulation, XVII: 1013-1019, June 1958)

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Change of Address

Please forward requests for change of address for the News Letter to: Commanding Officer, U. S. Naval Medical School, National Naval Medical Center, Bethesda 14, Md., giving full name, rank, corps, and old and new addresses.

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Myeloscintigraphy

The use of radioactive iodinated human serum albumin (RIHSA) in localizing lesions of the spinal canal has been described by Bauer and Yuhl in a preliminary report. Since June 1955, the authors have employed this technique for localization of lesions which show clinical evidence of spinal cord or root compression and varying degrees of spinal block.

The technique used is similar to that outlined by Bauer and Yuhl. If, at the time of the usual diagnostic lumbar spinal puncture there is evidence of a partial or complete spinal block, the isotope laboratory is called and approximately 300 μc of RIHSA in 5 cc. of normal sterile saline is injected before the spinal needle is withdrawn. If possible, the patient is placed in the knee-chest position for at least 15 minutes. If not, the foot of the bed is elevated. One hour after injection, the patient is scanned, using a commercially available, mechanical apparatus. The authors believe that this equipment is already somewhat outmoded.

The scintigrams obtained are referred to as myeloscintigrams. The myeloscintigram is orientated as to level by means of a lead marker placed on the patient's back, its location being identified on the scintigram. A roentgenogram of the involved area is made with the lead marker still in position. The scintigram is then superimposed upon the roentgenogram for localization of the spinal block. The authors noticed no significant untoward reaction in 28 patients subjected to this procedure.

Early cases in this series did not all have clinical evidence of a spinal block, but they are included for the sake of completeness. At the present time, the technique is usually reserved for those individuals with clinical evidence of either partial or complete spinal block.

Of the 28 patients studied thus far, 12 myeloscintigrams were reported as showing positive evidence of an abnormality, such as complete block, partial block, or interference with the circulation of the spinal fluid. Ten such reports were verified by operation. One was reported as showing a filling defect at the fourth lumbar inter-space, but laminectomy showed a herniated intervertebral disk at the fifth lumbar intervetebral space. The twelfth positive case was clinically diagnosed arachnoiditis and not operated upon.

Of 9 cases reported as negative, 2 were found to have small herniated disks at operation. One had diffuse arachnoiditis and the remaining 6 were not operated upon.

Seven myeloscintigrams were reported as uncertain. Six of these were considered to be suggestive of a spinal lesion. Three of the latter were operated upon and shown to have a lesion at operation. In the remaining 4, clinical evidence was not considered sufficient to warrant operation.

It is of special interest to note that in the 9 proved cases with evidence of partial or complete block at the time of spinal tap, the myeloscintigram

localization was correct in all, or 100%, of cases. In these cases, the authors believe their myeloscintigraphy to be of greatest value.

That myeloscintigraphy may ultimately prove to be of value in helping to establish the diagnosis of inflammatory as well as space occupying lesions of the spinal cord and canal is the belief of the authors. Further investigation of this possibility is at least indicated.

The simplicity of the technique makes it highly desirable and in this manner somewhat comparable to air myelography. Camp, in an excellent article on contrast myelography, has enumerated the advantages and disadvantages of air myelography; it appears to the authors—in their hands, at least—that myeloscintigrapny has fewer side reactions and will prove to be more satisfactory for the demonstration of partially obstructing lesions.

The average time required for scanning has been 25 minutes when 300 μc were used. Because the RIHSA is rather rapidly eliminated from the spinal fluid and excreted, there is no necessity to, or difficulty in, removing it as there is with potentially irritating radiopaque materials. The patient is much more comfortable during this procedure than during oil contrast myelography and there is no need for fluoroscopy. (Perryman, C. R., Noble, P. R., Bragdon, F. H., Myeloscintigraphy: A Useful Procedure for Localization of Spinal Block Lesions: Am. J. Roentgenol., 80: 104-111, July 1958)

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Cardiac Rehabilitation

Increasing interest in "cardiac rehabilitation" not only by physicians, but by public, governmental, and voluntary agencies has demanded that the medical profession give a satisfactory definition of this term. Direction is also needed for future energies to be expended in cardiac rehabilitation by those interested in this problem.

As part of a national survey of cardiac rehabilitation sponsored by the National Heart Institute, a questionnaire was sent to a number of the nation's leading cardiologists and internists who have had broad experience in cardiology, asking their definition of the term, their opinions as to how rehabilitation of the patient with cardiac disease is most effectively accomplished, and what future course should be taken in assuring the cardiac patient of his place as an effective member of society. The opinions of 36 of these physicians are contained in this article. It should be emphasized that these are doctors with consulting practices who daily face the problems of the patient with a diseased heart. The questions posed were:

1. What would you consider a proper definition of rehabilitation, especially as applied to persons with cardiovascular disease?

2. What do you believe are the major problems faced by the practicing physician in his efforts to rehabilitate individuals with cardiovascular disease?

3. What do you think should be done to solve some of these problems?

4. In the order of their importance, what measures have you found of value in the rehabilitation of your cardiac patients?

5. Please comment on your practical experience in the rehabilitation of patients with the following cardiovascular diseases: (a) congenital heart disease, (b) rheumatic heart disease, (c) hypertensive cardiovascular disease, (d) coronary artery disease, (e) cerebral vascular disease, (f) neurocirculatory asthenia, (g) iatrogenic heart disease, (h) syphilitic heart disease, (i) subacute bacterial endocarditis.

6. Give five or six examples of rehabilitation from your own practice.

A review of answers to the questions indicates that there is a fairly clear idea—in the minds of physicians at least—as to the meaning of cardiovascular rehabilitation. Also, it is evident that these practicing physicians believe that the most important factors in cardiovascular rehabilitation are: (1) proper medical treatment of the patient so far as disease processes are concerned; (2) the proper attitude of doctor and patient about the disease itself with emphasis on the possibility or probability of a return to a useful life and the elimination of fear concerning heart disease; (3) the need of correcting certain difficult customs and laws with respect to disability, compensation, and decision of unemployability by various industries; and (4) in apparently rare cases, the utilization of work classification units and their facilities for vocational counseling.

Rehabilitation has been proved possible in the majority of cardiovascular conditions, including congenital heart disease, rheumatic heart disease, hypertensive cardiovascular disease, coronary heart disease, and subacute bacterial endocarditis. There are two conditions in which this is still relatively difficult: cerebral vascular disease and neurocirculatory asthenia. However, emphasis should be put on the favorable longevity of individuals with neurocirculatory asthenia and the fact that they often "outgrow" some of their difficulty as they adjust themselves to their problems. All the physicians queried have had interesting experiences in the rehabilitation of their cardiac patients, the rehabilitation coming sometimes through the physician, but at other times, through the ability of the patient himself to adjust to his difficulties. (Williams B., White P.D., Lee, P.R., Rusk, H.A., Cardiac Rehabilitation - A Survey of Cardiologists' Opinions: Am. Heart J., 56: 107-111, July 1958)

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Use of funds for printing this publication has been approved by the Director of the Bureau of the Budget 19 June 1958.

Iron as a Therapeutic Agent in Pediatric Practice

This article discusses therapeutic uses of iron in light of current knowledge of iron metabolism and the author's experience in dealing with hematologic problems in pediatric patients.

Theoretically, iron should be administered only to prevent the development of iron deficiency. If early recognition of the several factors responsible for the development of iron deficiency was possible in each patient, preventive administration of iron would eliminate the deficiency states so commonly encountered in present day pediatric clinics. The conditions in which a physician might anticipate the eventual development of frank iron deficiency are listed in a table. In these situations, iron therapy is indicated for the prevention of clinical iron deficiency. If preventive administration of iron is not used, iron deficiency requiring appropriate treatment of the primary cause and administration of iron will be necessary.

That normal infants are born with sufficient iron to satisfy their needs for the first few months of life is generally accepted. The largest part of this iron reservoir is to be found at the time of birth in the circulating hemoglobin mass itself. The hematocrit—and particularly the red cell mass—per unit of body weight is significantly greater at birth than in older infants. As the fetal erythrocytes disappear from the circulation, iron is retained in the body and satisfies the larger part of the demands for iron of future growth. It is evident that any loss of infant blood prior to, during, or shortly after birth will deprive the growing infant of sources of iron that cannot be replaced from normal dietary sources.

Considerable controversy exists as to the significance of iron deficiency in the mother during pregnancy in the causation of iron deficiency in early infancy. In an American urban population, Lund and co-workers recently demonstrated a high incidence of iron deficiency during late pregnancy. How severe such a deficiency may be before the supply of iron to the infant is compromised remains an unanswered question. In the presence of a clinically apparent iron deficiency in the mother, administration of iron supplementation to the infant for 2 or 3 months early in life is recommended.

The Physicians' Desk Reference lists 170 preparations recommended as useful in the prevention and treatment of iron deficiency anemias. None is more effective than simple ferrous sulfate, most are more expensive, and many are more dangerous.

Either ferrous sulfate or ferrous gluconate is a suitable therapeutic agent. Ferrous sulfate is available in palatable concentrated form which can be administered in drop doses with symptoms of gastrointestinal intolerance encountered rarely in infants and young children.

The recommended therapeutic practice is to use simple ferrous salts in the prevention and treatment of iron deficiency states. A total dose of

60 to 75 mg. of elemental iron is given daily. The medication is given in at least two divided amounts each day to assure optimum absorption. The practice of giving gradually increasing doses of iron and administering the medication after meals is commonly advocated in adults where gastrointestinal intolerance to iron salts is not uncommon. With the ferrous sulfate concentrates available, gastrointestinal symptoms in infants or young children have not been commonly encountered even when starting therapy with full therapeutic doses and giving the medication to fasting subjects.

Less concentrated forms of iron in liquid form, such as elixirs of ferrous sulfate, have been found effective medications for use in infants and young children in the past. Staining of the teeth and the required 4 to 8 cc. doses which may be difficult to administer frequently to very young infants are distinct disadvantages to their use when compared to currently available iron concentrates. Where cost is a major factor in treatment, elixirs of ferrous sulfate will be found somewhat less expensive than the concentrated preparations.

In older children, tablets of ferrous sulfate (0.2 gm.) or ferrous gluconate (0.3 gm.) will often be more suitable than liquid preparations. One or two tablets are given 3 times daily providing a total daily dose of 220 to 440 mg. of iron. In older children, gastrointestinal symptoms of nausea, vomiting, or abdominal pain will occasionally be encountered if iron is taken when the stomach is empty. In addition, school-aged children will take the medication with more regularity if it is given at mealtime. For these reasons, iron tablets are best taken 3 times daily with, or immediately following, meals.

It is regrettable that all too often parents and physicians alike have a poorly controlled enthusiasm for injectable forms of medication. It is hoped that the enthusiasms for recently available injectable preparations of iron would be seriously tempered by the following well established facts regarding iron compounds now available for both intravenous and intramuscular injection.

Only a rare patient with iron deficiency anemia fails to tolerate and respond satisfactorily to iron salts given by mouth.

Toxic reactions following parenterally administered iron do occur and may occasionally be severe.

The body has no normal mechanism for the excretion of iron. Indiscriminate use of parenterally administered iron for long periods of use in patients not iron deficient may produce toxic iron-overload.

There is no increase in the rate of hemoglobin production in patients treated with parenteral iron when compared to those treated with oral iron that is clinically significant.

The response to iron therapy is highly predictable and will be manifest in an improvement in general well-being with rather prompt disappearance of symptoms of irritability and anorexia. Laboratory studies will show

a reticulocytosis in proportion to the severity of anemia present; a gradual predictable increase in hemoglobin concentration will result. The erythrocyte count will also increase.

Specific diagnosis is the keystone to successful and safe iron therapy. Chronic toxic iron overload is a potential danger in any patient being given iron in the absence of a proper diagnosis. (Smith, N. J., Iron as a Therapeutic Agent in Pediatric Practice: J. Pediat., 53: 38-50, July 1958)

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Sarcoma of the Mammary Gland

Primary sarcoma of the mammary gland has long been recognized as an infrequently occurring, but distinct, entity. The present study of the clinical and microscopic features of sarcoma of the breast was undertaken in an attempt to bring some clarifications to such factors as the history and physical findings, gross and microscopic pathologic observations, clinical course, and appropriate therapy associated with this type of primary neoplasm of the breast.

The records of all patients seen at the Mayo Clinic during the 50 years between 1907 and 1956 inclusive, whose diagnoses contained the term sarcoma in reference to a tumor of the breast, were selected for study. The histories and operative and pathologic reports were reviewed and abstracted. The gross and microscopic pathologic features of the available operative specimens were studied and evaluated. The presence of a benign epithelial component in a neoplasm, the stroma of which was richly cellular, indicated that the fundamental lesion was a fibroadenoma. Because the clinical course of fibroadenomas is benign, these lesions have been excluded from this study.

In 34 cases, there were microscopic features of the primary lesion which were consistent with a diagnosis of true primary sarcoma of the breast. The mean age of the 34 patients was 49.2 years, the extremes being 21 and 69 years. There were 33 women and 1 man in the series. The incidence according to side of the body was equal, 17 instances of the lesion having been noted on each side. The mean duration of the lesion as recorded in 28 cases was 55.05 months. A period of rapid growth averaging 4.25 months was noted in 18 cases. Antecedent trauma was a complaint in only 1 instance. Loss of weight just prior to the initial examination was noted in 6 patients, only 1 of whom had evidence of metastatic disease at the time of the complaint. Pain in the involved breast occurred in 14 of the 34 cases, but the detailed character of the pain was not recorded.

Retraction of the nipple occurred in 2 instances, in 1 of which this complication was bilateral. Fixation of the skin overlying the tumor mass was recorded in 10 instances. Change in color of the overlying skin had occurred in 7 cases. Ulceration of the overlying skin occurred in 3 patients.

Palpable ipsilateral involvement of the axillary lymphatic vessels were demonstrated in 10 of the 34 cases.

In general, the gross lesions were circumscribed, partially or wholly encapsulated, and irregular or lobed on the exterior surfaces. The size of the lesions varied, the extremes being 1.5 and 15 centimeters in diameter. The tumors generally were firm. The cut surface bulged, was smooth and glistening, either homogenous or whorled in appearance, and contained occasional areas of necrosis. Fixation in formalin had altered the natural colors of the tumors which were, therefore, not recorded.

Six groups of primary sarcomas of the breast were found in the 34 cases in this series. These groups were based on cell type and were classified as follows: fibrosarcoma, 14 cases; rhabdomyosarcoma, 4 cases; osteogenic sarcoma, 5 cases; liposarcoma, 1 case; malignant mixed tumor of breast, 5 cases; and mixed fibrosarcoma and carcinoma, 5 cases.

A period of latency or long duration prior to a period of rapid growth are two characteristics frequently associated with sarcoma of the breast. The duration of either or both of these characteristics obviously varies according to many factors.

Pain in the involved breast in more than one-third of the cases confirmed the impression of others that such a complaint deserves more than passing consideration by the clinician.

Fixation of the overlying skin in itself was found to be of little significance. The nature of the fixation was of some concern; in the majority of cases, it was described as being stretched or lacking mobility because of pressure and tension. The edema, orange-peel appearance, and retraction of the skin so frequently associated with carcinoma of the breast were lacking. Although actual involvement of the integument by the tumor process was not demonstrated in any of the cases in this series, it was reported by Gross.

The association of palpable involvement of axillary lymphatic vessels by primary sarcoma of the breast is of little significance because these tumors rarely, if ever, metastasize to regional lymph nodes. Smithy reported 32 cases in which mixed malignant processes of the breast were found to contain carcinoma as well as sarcoma. In Smithy's series, compiled from the literature, 11 instances were found in which axillary nodal metastasis by the carcinomatous element had been demonstrated. This observation obviously becomes significant in determining a course of surgical therapy in mixed lesions containing carcinoma.

The authors conclude that true primary sarcoma of the breast is a distinct clinical and pathologic entity, and that this lesion may contain one or more types of malignant mesenchymal tissue intimately admixed with malignant epithelial tissue. They further conclude that associated palpable involvement of axillary lymphatic vessels is of little significance in determining the appropriate surgical therapy or ultimate clinical course

associated with sarcoma of the breast. They are of the opinion that true primary sarcoma of the breast rarely, if ever, metastasizes to regional lymph nodes.

The authors suggest that primary sarcoma of the breast, although occasionally associated with ulceration, rarely invades the overlying integument, but that it is capable of metastasizing and often does metastasize, primarily by way of the blood stream, most frequently to the lungs. They believe that simple mastectomy with excision of the underlying pectoral musculature is adequate therapy for sarcoma of the breast not containing a malignant epithelial component, and that primary sarcoma of the breast which also contains demonstrable carcinoma in fresh-frozen sections should be treated by radical mastectomy. They are convinced that wide local excision—when feasible—is indicated in the treatment of recurrent sarcoma of the breast. (Botham, R. J., McDonald, J. R., Clagett, O. T., Sarcoma of the Mammary Gland: Surg. Gynec. & Obst., 107: 55-61, July 1958)

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Promethazine as an Adjunct to Obstetrical Analgesia and Sedation

The majority of obstetricians feel that analgesia and sedation are indicated during labor, but that routine measures for relief of the patient's pain are generally inadequate and dangerous to the infant.

Read's writings have revived interest in the psychological aspects of pregnancy and parturition, about which even yet very little is known. His method involves a system of prenatal indoctrination and a regimen of muscular exercises designed to allay the apprehension of the patient and to aid her in achieving voluntary physical relaxation during labor.

In this study, the authors have incorporated some of Read's prenatal indoctrination and have employed a different method of obtaining analgesia and sedation during labor. They have attempted to decrease the dosage of respiratory depressant drugs used and, at the same time, obtain what is considered safe and adequate analgesia and sedation with no detrimental effect upon the patient or infant.

Simple psychotherapy should be practiced as part of the prenatal program from the earliest visit to the physician. During pregnancy, the authors' patients make 12 to 14 visits to their office—more, if advisable. At each visit, after the routine examination has been completed, the patient returns from the examining room to the private office for a talk with her obstetrician. This verbal contact with the patient does more to establish rapport and dismiss the fearful unknowns of pregnancy than sending her home armed with printed literature only. Every effort is made to nurture in the patient a will to conscious participation in the birth process. The risk to the infant

of respiratory embarrassment from narcotics is stressed, as well as the fact that by insisting on delivery in the unconscious state, she is depriving herself of a profound experience to which she has a natural right. She is assured, however, that medication will be provided to relieve the most painful and exhausting phases, although a certain amount of discomfort cannot safely be avoided.

In the authors' practice, the results obtained with meperidine and scopolamine in the dosages usually employed have coincided with the experiences of many others. Especially in the conduct of prolonged or severe labor or in association with a general anesthetic for delivery, the well known depressant effects have been a handicap.

Previously, the authors used oral promethazine (an ethyl phenothiazine hydrochloride which differs from chlorpromazine in having a branched side chain and in lacking the chlorine atom on the phenothiazine ring) for control of nausea and vomiting in pregnancy. A soporific effect was a frequent observation. Attention, therefore, was turned to parenteral use of promethazine in the hope of developing a more satisfactory regimen for management of labor.

The present investigation was begun in May 1955 and is continuing. Up to the time of this report (January 1957), the series totaled 500 private patients ranging in age from 16 to 42 years, with an average of 27 years. About 50% were primiparas. Gravidity ranged from i to xiii, and parity from 0 to xi.

All of these patients—even the most stable—exhibited some degree of nervousness and apprehension on admission despite the careful prenatal instruction they had received. The younger primiparas particularly were disturbed by the discomforts attending the first stage. At the onset of each contraction, such patients without medication usually became tense and fearful in anticipation of the full impact of the pain regardless of reassurances and instructions to "relax."

In 75% of all patients at term, delivery was spontaneous; low forceps were used in 14%. Breech extractions were performed in 4%; and in 3%, rotation with Kielland forceps was necessary. Mid-forceps with manual rotation were used in 0.6%; and cesarean section was required after failure of trial labor in 0.4%. Seven pairs of twins and 9 single infants were delivered by breech extraction.

In 15 to 30 minutes after the first injection, a definite general relaxation was noticeable regardless of the size of the dose. On administration of subsequent doses, the onset of analgesia and sedation was even more rapid and the duration usually longer. Some patients dozed and others fell into a light sleep from which at times they awakened temporarily as contractions became more forceful. They could be aroused easily, answered questions intelligently, and cooperated in response to directions.

The great majority (88%) of the patients received adequate sedation with one dose consisting of 100 mg. promethazine, 50 mg. meperidine,

and 1/150 or 1/100 grain scopolamine, administered on dilatation of the cervix to 2 to 4 cm. A second dose, usually of 50 mg. of promethazine and 50 mg. of meperidine, but without scopolamine in some cases, was required by 10% in 3 to 5 hours after the first dose. Two percent of the patients required a third dose, averaging 50 mg. promethazine, 50 mg. of meperidine, and 1/200 grain of scopolamine about 6 hours after the second. Adequate analgesia and sedation were also provided by similar doses administered during a trial of labor which preceded one cesarean section in the series. The authors now routinely use promethazine 100 mg., meperidine, 50 mg., and scopolamine 1/150 grain, administered 2 hours before operation in all cases of elective cesarean section with excellent results.

The authors found analgesia and sedation predictable with this method and believe the measures described will stimulate an important change in the management of labor. The obstetrician will be obliged to devote a little more time to each patient during pregnancy, persuading her that delivery can be accomplished without narcosis, yet without excessive pain, and that the physical benefits to the infant are incalculable.

The influence of the premedication on the duration of labor appears especially noteworthy because it has been generally considered that normal labor averages about 17 hours in length.

Promethazine was administered to 500 private patients in an attempt to provide more adequate sedation in labor, yet avoid respiratory embarrassment in the infant. Premedication was first administered on dilatation of the cervix to 2 to 3 cm. In most cases, adequate sedation was obtained with one dose of 100 mg. promethazine, administered intramuscularly, with 50 mg. meperidine and 1/150 or 1/100 grain scopolamine injected in a separate syringe.

Labor in uncomplicated cases was definitely shortened. In 87% of the primiparas, labor was without complication; in 96% of these, delivery occurred in 1-1/2 to 7 hours after the first injection and 50% were delivered in a total of 3 to less than 8 hours. There was no respiratory depression in the infants as a result of the medication and, after a 2-year follow-up by their pediatrician, no delayed or unrecognized effect has been noted. (Gordon, L. E., Ruffin, C. L., Promethazine as an Adjunct to Obstetrical Analgesia and Sedation - A Series of 500 Cases: Am. J. Obst. & Gynec., 76:147-151, July 1958)

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Occupational Medicine Program - Scientific Assembly of American Medical Association

The Scientific Assembly of the American Medical Association convened in San Francisco, Calif., June 23-27, 1958. The Section on Preventive Medicine met on three successive afternoons. Occupational medicine was well

represented by such outstanding men as Robert A. Kehoe, Frank Princi, Rutherford T. Johnstone, Edward P. Luongo, and Edward J. Tracy—all holding offices in the Section.

The Program of the Scientific Assembly contained the following abstracts of papers presented at the joint meeting of the Section on Preventive Medicine and the American Academy of Occupational Medicine:

The Occupational Diseases: Diagnosis and Proper Method of Reporting

Statistics derived from the reporting of communicable diseases approach a high degree of accuracy. The information obtained serves to prevent or control such diseases. The primary objective of occupational medicine is likewise prevention. In most states, the law requires the reporting of an occupational disease, but unlike Public Health statistics, those obtained by state agencies about the incidence or cause of an occupational disease are almost completely worthless. Both the medical profession and the administrators of Workmen's Compensation are at fault. Because the law requires immediate reporting after the first examination upon a standard form of insufficient space, the physician is encouraged and yields to the conjectural type of diagnosis. State agencies and the Association of Industrial Accident Commissions should change the requirements to the narrative form of reporting. (Rutherford T. Johnstone)

The Physician as Advisor to Industrial Management

Industry provides a broad spectrum of opportunity for economic advancement to physicians generally. At the lower end is the simple arrangement requiring no unusual medical talent whereby a fee is derived from rendering an occasional technical service to an employee. In the middle range are the considerable benefits which the experienced industrial physician can derive from a career in occupational medicine devoted to the projection of a trained viewpoint. At the top of the spectrum are the rewards to the rarely available physician having a combination of imaginative, analytical, and administrative talents shaped by medical perspective and who becomes an integral member of top industrial management. Assuming basic professional competence and an inquisitive attitude, the physician who advances in industry does so in proportion to his skill in speaking to, with, and for management in medical concepts adapted to the occupational environment.

(Clifford H. Keene)

The Problem Back

The effect of significant actual trauma on spinal structures is not difficult to diagnose or to treat. Spinal tissues stretched, or disrupted, except nerve elements, heal by primary intention in a predictable length of time. The course of tissue healing is toward rapid repair and

improvement, not toward chronicity. The so-called "Problem Back" occurs only when the element of chronicity arises. The exaggerated symptoms and prolonged disability of the individual so affected makes an initial diagnosis of acute back sprain suspect. Chronic back complaints are most commonly due to either disease, structural abnormality, environmental conflicts, emotional attitudes, or a combination of one or more of these. In California, one-fifth of all cases of lost time are due to back injury and it is the most common single cause.

(John E. Kirkpatrick)

Hospital Employees: Corridor Consultations or Health Maintenence?

Only recently considered as industrial plants, hospitals have, in some instances, developed employee health programs. Whereas such preventive medical efforts progress without too much difficulty in manufacturing situations, the health service director in a hospital faces the competing practice of corridor medicine, and the frustrating poor documentation of the findings and recommendations resulting from this curbside consultation. An opportunity exists for the general practitioner to exercise preventive medical measures in the hospital setting, be it a small community installation or a large University Medical Center. As hospital employees usually are underpaid and have come from underdeveloped medical backgrounds, a strong positive program is needed, and the activity can be rewarding and satisfying.

(Jean Spencer Felton)
(OccMedDispDiv, BuMed)

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Expired Air Resuscitation

Extensive physiological measurements in 29 adult anesthetized patients demonstrated expired air resuscitation to be an efficient versatile method of artificial respiration. Reoxygenation of the patient's lungs is possible with four inflations, and within a circulation time, arterial oxygen saturation can be restored to normal. Carbon dioxide levels are concomitantly reduced. The data reported refute the widespread prejudice that a rescuer's exhaled air contains too little oxygen and too much carbon dioxide. By mild hyperventilation, the rescuer readily converts his exhaled air to a suitable resuscitating gas. He can perform the method for prolonged periods without undue fatigue or hypocapneic symptoms.

Experience with mouth-to-mouth techniques and its variants in emergency resuscitation of hospital patients and physiological measurements made under controlled conditions indicate that two important precepts must be followed: (1) A patent airway must be promptly established and maintained. (2) Inflation volumes of a liter or more must be delivered to the

adult victim's lungs at a rate of 12 to 20 per minute. (Elam, J.O., Greene, D.G., Brown, E.S., Clements, J.A., Oxygen and Carbon Dioxide Exchange and Energy Cost of Expired Air Resuscitation: J.A.M.A., 167: 328-334, May 17, 1958) (OccMedDispDiv, BuMed)

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Seminar in Aviation Medicine

The Third Annual Reserve Research Seminar in Aviation Medicine was held at the U.S. Naval School of Aviation Medicine in Pensacola, Fla., May 12-25, 1958. Thirty-three Reservists of the Army, Navy, and Air Force attended.

Among the attendees there were physicians, psychologists, basic medical scientists, engineers, and representatives of the professions of psychiatry, ophthalmology, dentistry, optometry, radiology, pathology, and electronics.

The purpose of these Seminars is to provide Reservists with a broad understanding of the personnel and operational problems of Naval Aviation, and its role in the conduct of modern warfare.

At the beginning of the Seminar, the Chief of Naval Air Training and his staff presented the logistics and training problems involved in the procurement, selection, training, and retention of Naval aviators capable of handling the complex expensive and "hot" aircraft now being delivered to the Fleet.

The physics of the upper atmosphere, outer space, and of satellite launching were presented. These were followed by discussions of the biological, physiological, and psychological problems which confront man in high speed, high altitude flight under all-weather and combat conditions. In addition, special presentations were made on the biological and psychological problems involved in the explorations of outer space.

Visits and informal discussions were held with small groups in the various research laboratories. These included physiology, biochemistry, low pressure, acoustics, radiation, electron microscopy, ophthalmology, and psychology.

The use of pressure suits to protect the pilot against gravitational forces in high speed maneuvers as well as in escape from aircraft at high altitudes was demonstrated. At the USAF Air Proving Ground Command, tests of planes and ordnance under climatic conditions simulating the tropics and arctic regions of the earth were observed. Small groups were led through a test hangar where six planes were undergoing tests at 65°F below zero. The change from 86°F outdoor temperature to this arctic cold in less than a minute was impressive.

Captain C.F. Gell MC USN of the Aeronautical Medical Equipment Laboratory, Philadelphia, Pa., described and showed movies of the

confinement of six volunteers for 7 days in a small cabin simulating conditions of space flight. Around-the-clock tests and measures were made of physiological conditions of the men and performance on psychological tests and problems of learning.

Commander G. W. Hoover USN discussed the ONR development program for a new electronic cockpit instrumentation and control system. This system provides the pilot with information permitting him to maneuver the aircraft under all weather conditions as if he were flying by visual contact on a clear sunny day. Radical new designs and miniaturization of components are major factors in making this design practicable.

The seminar was planned and conducted by Commander H. A. Imus MSC USNR, a member of Naval Reserve Research Company 5-10, Naval Medical Research Institute, Bethesda, Md. The Office of Naval Research, in conjunction with the Naval Air Training Command and the Naval School of Aviation Medicine sponsored the Seminar with the approval of the Bureau of Naval Personnel, the Bureau of Medicine and Surgery, and the Bureau of Aeronautics. (ONR)

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Environmental Sanitation Course

Applications are invited from Medical Service Warrant officers interested in assignment to duty under instruction in Environmental Sanitation at the University of California, Berkeley, Calif. This five-month course, commencing in January 1959, consists of full-time academic training in general sanitation, medical statistics, vector control, venereal disease control, bacteriology, and communicable diseases. Successful completion leads to designation and assignment as Environmental Sanitation Officer.

Applications must be submitted to the Chief, Bureau of Medicine and Surgery via the chain of command, to reach the Bureau no later than 15 August 1958. The following information is required in each application:

1. Statement of total service
2. Resume of academic background
3. Obligated Service Agreement (as set forth in paragraph 8a. of BuMed Instruction 1520. 12)

It is highly desirable that a copy of all transcripts of formal college training be submitted with the application unless these have been furnished previously to the Bureau. Should the deadline of 15 August prevent submission of transcripts to accompany the request, such transcripts may be forwarded as soon thereafter as practicable. Dispatch requests may be submitted if necessary to meet the deadline, but must be confirmed as soon as practicable with complete letter application. (MSC Div, BuMed)

MSC Training in Navy Management

Early applications are desired from eligible Medical Service Corps officers interested in attending the Navy Management course convening in January 1959 at the U. S. Naval Postgraduate School, Monterey, Calif. This five-month course is designed to provide executive development education at the postgraduate level. While it is desirable that applicants hold a bachelor's degree from an accredited educational institution, this is not required. Two (2) officers of the Supply and Administration section have completed this school successfully, and it is planned to enter two (2) in each convening class (January and August) so long as quotas are available.

Applications for this full-time in-service program must be submitted to the Bureau via the chain of command, and should be received no later than 15 August 1958 for favorable consideration. Eligibility requirements and application procedures are contained in BuMed Instruction 1520. 12. Dispatch requests may be submitted if necessary to meet the deadline, but must be confirmed as soon as practicable with complete letter application including the required obligated service agreement. (MSC Div, BuMed)

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From the Note Book

1. A recent directive authorizes the appointment of a civilian physician as deputy director of the Armed Forces Medical Publication Agency and associate editor of its publications. Applicants must be citizens of the United States; be graduates of approved medical schools in the United States or Canada; have completed a one-year accredited internship; have at least 2 additional years of clinical experience, and a minimum of 5 years experience in medical editorial work. Full time residence in Washington, D. C. is also required. A Civil Service grade up to GS-15 with a salary range up to $13,970 has been established for the new position. Physicians interested in this position should make informal application to the Director, Armed Forces Medical Publications Agency, 2300 E. St., N. W., Washington 25, D. C. (A. F. M. P. A.)

2. The Secretary of the Navy has approved insignia for wear by personnel in pay grades E-8 (senior chief petty officer) and E-9 (master chief petty officer). Personnel in pay grade E-8 will wear a rating badge consisting of the present chief petty officer's rating badge with one star worn above the eagle's head. Personnel in pay grade E-9 will wear a rating badge consisting of the present chief petty officer's rating badge with two stars arranged horizontally above the eagle's wings. This change will be promulgated in a future change to U. S. Navy Uniform Regulations. (Navy Dept. Office of Information)

3. Twenty-three prominent physicians, nurses, social workers, hospital administrators, and public health officials met in Roanoke, Va., June 9-13, 1958, at the invitation of the Public Health Service to consider organized home care programs in the United States. Citing the fact that there are now approximately 50 programs functioning in this country which provide coordinated health services to patients in their own homes, the group urged more widespread development and support of such community programs by Federal, State, and local health and welfare agencies; the health and health-related professions; and health insurance agencies. (PHS, HEW)

4. Nitrate blood levels can be influenced by nitroglycerin or pentaerythritol tetranitrate (PETN). There is an abrupt rise and fall in nitrate blood levels following administration of each dose of PETN in tablet form. By combining PETN in timed-disintegration capsules, a more uniform release of the drug is obtained. PETN provides a uniform sustained release of the drug and a prophylactic effect for 10 to 12 hours' duration in the treatment of angina pectoris. (Circulation, June 1958; J. W. Berry, M. D., T. C. Roach, M. D.)

5. The hemiplegic patient is capable of unrealized restoration from a physical, mental, and social level. When an integrated plan of treatment involving medical, neurosurgical, physical, psychological, and vocational aspects is applied, at least 90% of hemiplegic brain-damaged patients are amenable to rehabilitation in its various goals. (Radiology, June 1958; M. K. Newman, M. D., B. Jewett, M. S., G. Frampton, B. S.)

6. The outlook for patients with paralysis agitans is much brighter. There is a much wider and safer selection of drugs to combat the symptoms of idiopathic and arteriosclerotic cases. Surgical procedures are being applied with greater skill and better understanding and they harbor brighter prospects of relief to the patients. (J. A. M. A., 5 July 1958, L. J. Doshay, M. D.)

7. Chronic nonspecific pneumonitis is a definite entity that can be diagnosed clinically and roentgenographically. The initial treatment should be medical. For those cases failing to respond to intensive medical therapy or that recur promptly when medical therapy is discontinued, pulmonary resection becomes the treatment of choice. (Ann. Int. Med., June 1958; W. R. Deaton Jr., M. D.)

8. A Public Health Service study among nearly 200,000 U. S. veterans shows a significantly higher death rate among regular tobacco smokers than among nonsmokers. The first report on the extensive and continuing statistical survey was made to the Seventh International Cancer Congress in London. The survey generally supports the findings of earlier studies demonstrating

a statistical relationship between death rates and smoking. The study did not include clinical or laboratory research. (PHS, HEW)

9. There is no simple formula for management of rubella in pregnancy. All factors must be carefully considered and each case carefully evaluated on an individual basis. At the present time, the prevention of congenital malformation caused by rubella can best be achieved by deliberate exposure of young girls to the disease. In this manner, they may acquire a durable immunity that will protect them during their childbearing period. (New England J. Med., 3 July 1958; S. Krugman, M.D., R. Ward, M.D.)

10. Nine ovarian carcinomas of presumed mesonephric origin are reported. These tumors are characterized by tubular structures which often resemble wolffian duct tubules. Branching dichotomous tubules may prove to be a prominent feature. These neoplasms are malignant and when they arise in the ovary, presage a grave prognosis should capsular invasion and adherence to adjacent structures be present. (Surg. Gynec. & Obst., July 1958; S. Kay, M.D., R. H. Hoge, M.D.)

11. The "flat top and V" pattern of the electrokymogram in chronic constrictive pericarditis is discussed as well as the opinions expressed by various authors in regard to this finding. The findings obtained by analytic roentgen kymography in 16 cases of chronic constrictive pericarditis are reported. (Am. Heart J., July 1958; A. Laconi, Palermo, Italy)

12. A technique for evaluating the effects of heart-valve surgery while an operation is in progress has been developed by a team of surgeons and cardiologists at the National Heart Institute. With this technique, direct measurements are made of the heart's output of blood and of differences in pressure on each side of abnormally narrowed, or "stenosed" valve openings just before and after these openings are surgically enlarged. The new technique allows a more precise and immediate evaluation of the results of heart valve surgery than has previously been possible with conventional techniques by which pressures and output of blood are measured before and after an operation, but not during the operation. (PHS, HEW)

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Ristocetin - Effects and Side Effects

During an 18-month period, 37 cases of staphylococcal pneumonia were encountered in a Naval Hospital. Treatment was complicated by the emergence of staphylococcal strains almost totally resistant to available antibiotic agents.

Ristocetin became available early in this experience and was administered to 17 patients, from nearly all of whom antibiotic resistant staphylococci were isolated. Two additional patients were given ristocetin during the moribund state. In all, there were three deaths in the entire series of 37 cases. It is the purpose of this communication to report the effectiveness of this new agent and to emphasize precautionary measures to be observed in its administration.

The dosage for the majority of staphylococcal infections is 25 mg/Kg. daily. Because the antibiotic is excreted mainly via the kidneys, it should be administered with caution in patients with a renal impairment. In these cases, the antibiotic may accumulate in the body fluids with an increased likelihood of toxic effects. This restriction also applies to infants and patients aged more than 65. In these groups, it is recommended that the dosage should be reduced by 25 or 50%.

Leukopenia and neutropenia have been reported as complications of ristocetin therapy. In all cases, there should be a frequent determination of blood count with particular reference to the total leukocytes and the percentage of polymorph neutrophils.

Method of administration. The drug was available in 500 mg. ampoule units, and the required amount was dissolved in 30-100 ml. of 5% glucose and administered over a period of 10 to 30 minutes in 2 to 4 divided doses. The solution was injected into the tubing of an intravenous infusion system (5% glucose). One hundred to two hundred ml. of glucose solution was flushed through the tubing at termination of drug injection. According to experience, this more rapid method of administration resulted in less local irritation.

To minimize toxic side effects, careful attention to dosage and technique of administration is mandatory. Effects on the hematopoietic system are not common, but are more likely to occur when dosage exceeds 25 mg.Kg per day.

Blood counts—with particular attention to the white blood cells and platelets—are recommended on alternate days during therapy. Depression of the white cell count should call for a reduction in dosage, or withdrawal of therapy in severe cases.

Because ristocetin is excreted by the kidney, renal integrity should be appraised in every instance. Patients with renal impairment, the very old, and the very young should all receive a reduced dosage.

With observance of the foregoing precautions, ristocetin has served as a safe and potent anti-Staphylococcal agent. (Captain G. L. Calvy MC USN, Lieutenant L. R. Schumacher MC USN, U. S. Naval Hospital, St. Albans, N. Y.)

(Refer to Medical News Letter, Vol. 31, No. 4, Page 13)

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DENTAL SECTION

Erroneous Submission of Supplement to Dental Service Report

Some dental activities have erroneously submitted the Equipment and Facilities Supplement to the Dental Service Report (DD-477-1) for the period ending 30 June 1958.

Attention is invited to Article 6-150 (3) (b), Chapter 6 (Revised), Manual of the Medical Department, which states that the DD 477-1 shall be submitted as of January 1 each year. Submission as of July 1 is not required.

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Casualty Treatment Training to be Exhibited in Brussels

Captain V. J. Niiranen DC USN, Head, Training Aids Department, U. S. Naval Dental School, National Naval Medical Center, Bethesda, Md., will monitor the U. S. Navy "Casualty Treatment Training Program" exhibit at the Federation Dentaire Internationale in Brussels, Belgium, during August 28 to September 3, 1958.

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RESERVE SECTION

Credit for Attending Professional Meetings

The Chief of Naval Personnel has authorized retirement point credit for each of the below listed professional meetings and symposium to be conducted on the dates listed. Eligible Naval Reserve Medical Department officers must register with the military representative present. Security clearance is not required.

Annual Meeting, American Psychological Association. Hotel Statler, Washington, D. C., 26 August - 3 September 1958

This meeting, having military significance for those inactive Reserve Medical Department officers whose specialty is psychology, will present lectures and discussions which will provide information and techniques employed in psychology that are not readily available to these officers in their civilian pursuits, but invaluable to their respective functions in the event of mobilization.

Fourth Naval District Ninth Annual Military Medico-Dental Symposium. U. S. Naval Hospital, Philadelphia, Pa., 22 - 24 October 1958.

Under the sponsorship of the Commandant, Fourth Naval District, this symposium has as its theme "Space Medicine" and will be presented by speakers and discussants of outstanding prominence in their specialties. Addresses will be given by the Honorable Frank Berry, Assistant Secretary of Defense (Health and Medical) and Doctor Wernher von Braunn, Director, Development Operations, Army Ballistics Missile Agency, Redstone Arsenal, Huntsville, Ala. This symposium is presented for the benefit of Medical Department personnel of the Armed Services, both active and inactive.

65th Annual Convention of the Association of Military Surgeons, Hotel Statler, Washington, D. C., 17 - 19 November 1958.

The theme of this meeting is "Dynamic Medicine and Rehabilitation in the Space Age" and will present subjects which will afford those in attendance an excellent opportunity to remain abreast of the latest developments in military medicine. The Assistant Secretary of Defense (Health and Medical) has endorsed this convention as suitable training for inactive Reserve Medical Department officers of the Armed Services.

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Medical Ensign USNR Designator Changed

Formerly known as Ensign 1995 (Medical) officers, undergraduate medical students holding commissions in the Navy's Ensign Medical Program now have a new designator - "1915." This change contained in BuPers Instruction 1210.4B of 31 May 1958 also provides a new designator for dental students - "1925," and theological students - "1945." Prior to 31 May 1958, student officers in medical, dental, and theological schools were assigned the numerical designator 1995 followed by their particular staff corps title.

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Contingency Option Act and Aid to Dependents

If you are nearing completion of 18 years' service creditable for basic pay, you may want to take a look at the provision of the "Uniformed Services Contingency Option Act."

This Act which applies to Reserve and Regular officers and enlisted personnel allows you to provide an income for your survivors by electing to receive a reduced amount of retired pay. In this manner, you may provide an annuity equal to one-half, one-fourth, or one-eighth of the reduced amount of retired pay. The Act provides for four types of annuities.

If you want to provide this benefit for your survivors, you must make the election before you complete 18 years of service for basic pay purposes. These 18 years, therefore, are not limited to "years of satisfactory Federal service."

Complete information on the Act may be found in BuPers Instruction 1750.2. In addition, Reservists may obtain a booklet, Percentage Cost Tables for Selection of Options under the Uniformed Services Contingency Option Act of 1953, NavPers 15866, from their District Publications and Printing Office at no cost. (The Naval Reservist, June 1958)

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PREVENTIVE MEDICINE SECTION

The Seventeenth Veterans Administration-Armed Forces Conference on Chemotherapy of Tuberculosis

Twelve years ago, when streptomycin first became available for the treatment of tuberculosis in man, a nationwide cooperative study group was formed of Veterans Administration (VA) tuberculosis hospitals using this antibiotic. Its purpose was to learn, while this powerful newly discovered antituberculous agent was being used, about dosage, therapeutic effect, toxicity, and the best methods and optimum duration of its administration. The present cooperative study group with interests in all phases

of chemotherapy of tuberculosis includes 56 VA hospitals and 4 hospitals from the three branches of the Armed Forces. Participation as a study unit is entirely voluntary as is cooperation in any or all of the individual studies. A cooperation unit by volunteering to engage in a particular study agrees to treat all suitable patients by a certain regimen or to allocate them randomly between certain mutually agreed-upon regimens. Randomization is effected by a sealed-envelop system. All cases are reported on standardized forms from which data are transferred to IBM cards and tabulated to provide maximum information. Annually (usually in February), representatives from the study units meet to discuss the results of the previous year's work and to plan projects for the following year. The 1958 meeting—the seventeenth of these conferences—was held in Memphis, Tenn., February 3-6, 1958. Attendants and participants included 100 VA representatives, some 350 physicians and scientists, and a number of distinguished visitors from abroad, perhaps the most significant of whom were two representatives of the British Medical Research Council who acted as official liaison between the two tuberculosis research groups on either side of the Atlantic.

Various related papers, discussions, and future cooperative plans are summarized under 16 appropriate headings to provide in brief the results of this Conference.

STREPTOMYCIN administered daily combined with isoniazid and with isoniazid and para-aminosalicylic acid (PAS) was evaluated by the study units during the past 2 years. General regimens had been designed to answer the following questions: "In patients with no prior chemotherapy, what is the comparable therapeutic efficacy of daily streptomycin and isoniazid as compared with isoniazid combined with PAS?" and secondly, "Does the addition of a third drug (daily streptomycin in combination with both isoniazid and PAS) contribute anything to the therapeutic efficacy, also considering factors of toxicity and emergence of resistance?" During this interval over 1000 cases of pulmonary tuberculosis had been randomly allocated among 3 regimens: streptomycin, 1 gm. daily, combined with isoniazid, 300 mg. daily; isoniazid, 300 mg. daily combined with PAS, 12 gm. daily; and all 3 drugs in these dosage schedules. The groups were approximately equal in number and the patients in each group showed similarity in such background factors as age, degree of disease, and size and number of cavities. Therapeutic results were also very similar in more than 600 patients who had been treated for periods long enough for evaluation. These results were measured in such terms as x-ray improvement, disappearance of tubercle bacilli from sputum or gastric contents (proved by culture), and closure of cavities of varied sizes. Various inter-regimen differences were not significant when evaluated at 4-month or 8-month end points.

Bacterial resistance was slight (of those with positive sputum, bacilli were fully resistant in 3 to 4% and partially resistant in 6 to 9%), and identical

in the 3 regimens. Toxicity was least with isoniazid and greatest in the "triple-drug" regimen—7% had to stop PAS and 14% had to stop streptomycin. From these results, one might conclude that in all probability triple-drug therapy, even with daily streptomycin, had no special value from the therapeutic standpoint or from the standpoint of the prevention of bacterial resistance, and that this regimen had the drawbacks of greatest toxicity, greatest difficulty in administration, least suitability for outpatient treatment, and greatest danger of multiple-drug sensitization. Daily streptomycin seemed not to be superior to daily PAS as a companion drug to isoniazid. It was suggested that triple-drug therapy might find its greatest usefulness in the early treatment of a patient who had had previous drug therapy and who might have bacteria partially resistant to one or more of the three drugs. The study units decided to continue these regimens for a further brief period to obtain for treatment a sufficient number of the most critical cases—those with large cavities—and thus to give solid statistical significance to the absence or presence of inter-regimen differences. The daily use of streptomycin was associated with a moderate amount of damage to the eighth cranial nerve, especially noted in men past the age of fifty, necessitating discontinuation of the drug. Several studies in which dihydrostreptomycin pantothenate was tested against dihydrostreptomycin sulfate gave somewhat contradictory results. Two of these were reported as showing no indication that this new preparation was less ototoxic. Two other studies indicated that it might be less toxic. In discussion, streptoduocin was reported as being less ototoxic when used daily than either streptomycin or dihydrostreptomycin.

ISONIAZID has established itself as the most powerful agent in the treatment of tuberculosis and as an almost indispensable senior partner in all combined regimens; however, many questions still remain to be answered about its most efficient use. Previous evidence suggested that isoniazid alone might be an effective agent for the treatment of lesions of tuberculosis in which there is a minimum of tissue destruction and, therefore, the likelihood of the emergence of resistant bacilli is slight. Accordingly, the study units have been randomly distributing minimal cases and moderately advanced noncavitary cases between isoniazid alone (300 mg. daily) and in combination with PAS. The results to date in 150 cases reported upon reveal that x-ray improvement, sputum "conversion," and achievement of the "target point" occurred equally often in both groups. In addition, isoniazid alone was better tolerated and because only one patient in each group shed isoniazid-resistant bacilli it did not seem inferior in this respect. Thus encouraged, the study units voted to enlarge this randomized study and to make similar investigation of patients with tuberculous pleural effusions.

At the other end of the spectrum, two reports were presented to indicate that larger doses of isoniazid (10 to 18 mg. per kilogram of body weight)

with PAS (and pyridoxine or vitamin B_6 to prevent peripheral neuropathy) or high isoniazid dosage with daily streptomycin (with or without PAS) may be more effective than the commonly used doses of 4 or 5 mg. per kilogram. With high isoniazid regimens, sputum conversion was generally reported as being over 95%. Other evidences of improvement were impressive, although many cavities remained open. To date, however, no randomized studies have been done comparing the two isoniazid dosage levels. There was no INH (isonicotinic hydrazide) toxicity when pyridoxine (50 to 100 mg. daily) was administered. Spurred on by these favorable results, the study units plan to evaluate regimens in which "high" and "low" isoniazid dosage schedules will be the major variable with PAS as the companion drug.

The subject of isoniazid-resistant bacilli is of great interest because of the generally lowered virulence of this variant in animal experiments and perhaps for human beings. That it is virulent for man cannot be questioned; however, 1 or 2% of all newly infected persons who have never had treatment with this drug shed resistant bacilli, and by far the greatest likelihood exists that these infections were incurred by contact with persons in whom resistant bacilli developed as a result of previous isoniazid therapy. Studies with resistant bacilli in monkeys indicate that occasional isoniazid-sensitive mutants—with correspondingly high virulence—may develop in animals' lungs, revealing the possible mechanism of the development of resistant strains in human beings under isoniazid therapy.

CYCLOSERINE used alone proved to be a rather weak but, nevertheless, effective agent. A regimen containing isoniazid, 300 mg. and cycloserine, 500 mg., (in 309 patients, all with cavity formation) was compared by randomization with isoniazid in combination with PAS. Although good results were obtained from both combinations, patients receiving isoniazid combined with PAS had less evidence of x-ray worsening. This was calculated as a "risk" of 12% in 8 months in the isoniazid-cycloserine group as compared with only 1% in the others By other criteria (cavity closure, sputum conversion, and the development of isoniazid-resistant bacilli) the group receiving the combination with PAS showed slight but consistent superiority. With the 500 mg. daily dosage of cycloserine (250 mg. twice a day) no convulsions were noted; therapy was discontinued in one case because of optic neuritis and in two because of emotional or neuropsychiatric upsets. PAS toxicity caused three times as many patients to be dropped from the study as cycloserine toxicity. Two brief reports indicated that cycloserine, alone or with viomycin, could be of value in an occasional patient with advanced disease who had failed to respond or who had relapsed after months or years of treatment with more generally used drug regimens. Experiences with hospitalized psychiatric patients proved that—contrary to earlier recommendations—the mental condition is not a contraindication to, nor is it made worse by, the use of cycloserine.

PYRAZINAMIDE and isoniazid, 300 mg., were combined in regimens (one with a 3 gm. dose of pyrazinamide and one with a 1.5 gm. dose) for comparison with the combination of isoniazid and PAS. All patients included had cavitary cases. In terms of therapeutic effect, the combinations of isoniazid with PAS and with 3 gm. of pyrazinamide were approximately equal, but hepatotoxicity (which occurred in 10% and consisted chiefly in abnormal liver-function tests) was a disturbing factor in the pyrazinamide group. When the daily dosage of pyrazinamide was cut from 3 to 1.5 gm. and evaluated in a smaller group of patients, the therapeutic effect was about the same, but toxicity was only one-third as great. It is believed that the results warranted a more extensive evaluation of 1.5 gm. of pyrazinamide as a companion drug to isoniazid and plan to randomize cavitary cases between this regimen and isoniazid combined with PAS.

PARA-AMINOSALICYLIC ACID, acting together with isoniazid, has a powerful antituberculous effect; no other regimen has been shown to be consistently superior in terms of lowered bacterial resistance, cavity closure, or conversion of sputum bacteriology. Problems of particular interest centered upon gastrointestinal toxicity and the use of a single dose of 6 gm. daily rather than 12 gm. in divided dosage. In guinea pigs, a single daily dose was found as effective as the same daily amount divided into 2 doses; two single doses were as effective as 10 to 12 times as much given in the diet. In the treatment of a group of patients, when a single daily dose of PAS (approximately 6 gm.) was combined with streptomycin or isoniazid, therapeutic results were equal to those with larger total (but divided) daily doses, bacterial resistance was slight and drug tolerance was superior. No uniform superiority in PAS tolerance could be demonstrated when comparisons were made between sodium, potassium, or calcium PAS and Rezipas—patients were found with gastrointestinal intolerance to each of these, but could take some other preparation. There seemed to be no relation between the tolerance and the blood levels or free-acid equivalent. Least over all intolerance was obtained with one daily dose of 6 gm. of Rezipas. Evaluation of streptomycin will be continued twice weekly using sodium PAS in two dosage schedules of 12 gm. daily (divided into 3 doses) and 6 gm. in a single dose.

STREPTOVARICIN, an antibiotic, was used for the retreatment of patients revealing cavitation and tubercle bacilli susceptible to isoniazid. The daily dose was 3 gm. orally in a single dose with isoniazid, 100 mg., three times a day. Of 26 patients reported, 10 became isoniazid resistant at the end of 4 months and the therapeutic effects were considered equal to those of isoniazid alone. Such symptoms as lethargy, anorexia, and nausea caused considerable difficulty. No further study of this drug is planned.

THIOCARBANIDIN is tuberculostatic; its action appears to be of the same order as that of PAS, but is apparently produced in vivo in much smaller doses. In guinea pigs, it was definitely effective in prolonging the lives of animals and in lessening the amount of tuberculosis that did develop, but much less so than effective amounts of streptomycin or isoniazid. It appeared to reinforce the effects of small doses of streptomycin. Resistance to it was developed (in vitro) and the organisms then revealed cross resistance with amithiozone (TB_1, tibione). When used in 16 patients (as Thioban) in dosages of 0.25 gm. twice a day to 0.5 gm. four times a day, there were no evidences of toxicity to the bone marrow, kidney, thyroid gland, or liver. Therapeutic effects could not be evaluated adequately and further study of this drug is planned. At present, its most suggestive use is perhaps as an alternative drug for PAS in combined chemotherapy, but there is far too little experience with it at present for even a tentative appraisal of its future value.

KANAMYCIN, a new antibiotic, appeared to be less effective in guinea pigs than streptomycin with which, however, it demonstrated appreciable additive (or synergistic) effect. Used intramuscularly (absorption via the oral route being slight) it was not toxic for guinea pigs, but revealed some renal toxicity in human beings. High bacterial resistance developed in vitro after but four transfers and crossresistance to neomycin was observed. Its toxicity for guinea pigs, however, was insignificant compared to that of neomycin. Further evaluation of kanamycin is planned.

Photochromogenic Pathogens

Further reports were made on infections with acid-fast (but not clearly Mycobacterium tuberculosis) bacilli. Infections with photochromogenic bacteria (which become pigmented deep yellow or orange when growth continues after exposure to light) are especially common in the Middle West, and non-photochromogenic "atypical" or "anonymous" infections are especially common in the Southeast. These photochromogenic bacilli all show certain characteristics: a negative Konno niazin test, growth in room temperature high pretreatment resistance to PAS, isoniazid, and streptomycin, especially to PAS, and guinea pig virulence. Forty-nine cases due to this organism were reported from Cook County, Ill. During a 3-year period, of 929 "positive" cultures for tubercle bacilli, 32% were atypical; in 49 patients, photochromogens were the only bacilli recovered and they were believed to be the cause of the pulmonary disease noted. These cases were heavily concentrated in 3 contiguous communities in a small area west of Chicago that contributed 63% of the photochromogenic cases, although only 19% of the cases of tuberculosis. There were no evidences of intrafamily contagion; indeed, family contacts had a low prevalence of tuberculin reactors. The lesions tended to be fibrotic and fibrocavitary; exudative, caseous, acute

inflammatory or extrapulmonary manifestations were not observed. The organisms showed high resistance to PAS and moderate resistance to streptomycin and isoniazid. Response was slow to treatment with high isoniazid dosage, and surgical complications with resection were very frequent (40% as compared to 9% in typical tuberculosis). The exact nature of this disease or of these bacilli is not known. The adjective "anonymous" was suggested as preferable to "atypical" which implies that these are a variant of some "typical" organism, such as Myco. tuberculosis, and present information suggests that they are not.

Infection with Resistant Tubercle Bacilli

At the 1957 conference, 4 studies were analyzed to reveal that apparently about 2% of all patients with untreated tuberculosis will have organisms reported as resistant to isoniazid or streptomycin. This still obtained with some variations, but with no appreciable annual increase. These conclusions were drawn from 3 separate reports involving approximately 8000 cases in the United States and 1000 in Great Britain. Just how many of these infections were due to contagion previously treated, but still infectious cases, is not known. It was suggested that completely new—primary—cases should be carefully analyzed for possible evidence of an increasing rate of infection with resistant bacteria.

Follow-Up Studies

In the prechemotherapy years, the relapse rate of tuberculosis was high in cases classified as "arrested" by National Tuberculosis Association (NTA) standards. Several papers described follow-up studies in a large number of patients treated by chemotherapy with and without thoracic surgery. Some 900 patients followed for 3 years after discharge as "arrested" or "inactive" from a VA Hospital revealed that. of those discharged between 1947 and 1952, 30% relapsed; in the next 2 years, this figure dropped to 14% concomitant with the introduction of isoniazid and of continuing outpatient treatment. Most of the relapses responded well to a second course of chemotherapy. Of 2500 patients discharged from an Army Hospital from 1951 to 1956 and followed for 1 to 5 years, only 4% relapsed. Two hundred and twenty-six patients with pulmonary resection at another VA Hospital followed for 1 to 7 years (145 for 3 years or longer) revealed 8 relapses (3.5%), only 2 while the patients were still on drug therapy. Patients with open cavity and positive sputum at the time of surgery had a 7.5% relapse rate (chiefly in patients with drug-resistant bacteria). All relapses occurred in patients who had active disease with caseation in the removed specimen and in whom residual disease was to be expected on the basis of the preoperative x-ray study. All reactivation of the disease occurred at, or near, the site of preexisting disease.

Thoracic Surgery

Combined with chemotherapy, surgical collapse and resection were performed in many patients. A series of 142 thoracoplasties done between 1946 and 1950 revealed 62% successes at the end of one year with a gradual increase in relapses so that 7 to 11 years after operation, 44% of patients were well and 10% were dead of tuberculosis or pulmonary insufficiency—the larger the cavity, the worse the result. In a recent series, 1951 to 1955, the results were found to be even worse because these were generally the "salvage" patients who had resistant bacilli, could not withstand resectional surgery, et cetera. In the "open-negative" cases, thoracoplasty was effective (in 86%) as a definitive surgical measure. The use of extraperiosteal collapse with Lucite spheres or Ivalon sponge plombage was reported as an effective collapse measure for cavitary disease where a cavity of moderate size is located high in the lung field. It is indicated in older patients with limited pulmonary reserve and in bilateral disease when bilateral resection is thought to be too hazardous. This form of collapse appeared to be effective in many cases that did not seem amenable to other surgical measures; resection was quite feasible later in many of the failures. In the absence of infection, the plomb was generally left in permanently; however, considerable difference of opinion and experience exist as to its advisability.

Analysis was made of the surgical experiences of 44 hospitals contributing statistics to the Conference. Some 1300 cases of excisional surgery were reported and comparisons were made with previous years. These indicated a decrease in segmental and subsegmental resections with no change in pneumonectomies and some increase in lobectomies. Bronchopleural fistula—by far the most serious and frequent complication—occurred in 14% after pneumonectomy, 7% after lobectomy, and 4% after segmental surgery. Surgical death rates were 15% after pneumonectomy, 4% after lobectomy, and less than 1% after segmental surgery. When the risk of pulmonary resection was correlated with preoperative sputum status, it was found that the risk of empyema and of postoperative death after lobectomy and pneumonectomy was appreciably higher in the sputum-positive group. This did not hold in segmental reactions. The opinion was expressed that resistant bacilli and copious sputum added to this hazard. Active tuberculosis after resection was attributed to residual nonresected lesions, residual bronchiectasis, bronchopleural fistulas, sutures in the bronchi, wound infections, and in 33% there were no obvious causes. The majority of "failures" became inactive with further drug therapy or further surgery. Of 2326 resected cases, 90% of the patients who had but one resection were well; when a later contralateral resection was needed, only 50% were well. The late reactivation rate was 6 to 9%; preoperative duration of drug therapy had no noticeable effect upon this late relapse.

Corticosteroid Therapy

Much discussion about this subject revealed that the steroids are beneficial when used in ample dosage for seriously ill patients with tuberculosis, whether meningeal or otherwise. If effective antituberculous drugs are also used and the steroids tapered off rather than stopped abruptly, this is believed to be safe in all cases and perhaps life-saving in many. A preliminary report was made of a British Medical Research Council project (begun in October 1957) in which all included patients with pulmonary tuberculosis will receive streptomycin, PAS, and isoniazid; in addition, in a double blind study, one-third will receive ACTH for 3 months and one-third will receive prednisone; the remainder will serve as controls. The study units recommended no general steroid study, but will volunteer individual research designs to evaluate this problem.

Duration of Chemotherapy

Patients are being randomized after reaching the "target point" (sputum conversion, cavity closure, and stable x-ray appearance) between two regimens: chemotherapy (any effective drugs) for an additional 9 months, and chemotherapy for an additional 18 months. As yet, this study has not been in existence long enough for evaluation. Its purpose is to determine what benefit, if any, upon relapse rates chemotherapy provides when continued well beyond the point of inactivity (according to NTA standards).

Fungous Infection

Of much interest were several reports on amphotericin B. In the treatment of cryptococcal meningitis, 7 of 9 patients are alive and 6 have negative spinal fluid cultures. This drug has also been used in coccidioidal meningitis with early promising results. Serologic surveys for histoplasmosis have revealed a very large percentage of positive reactors in tuberculosis hospitals, especially in the endemic areas. Such tests have helped in the detection of new cases and in the diagnosis of pulmonary problems. Special cooperative study groups now exist for blastomycosis, histoplasmosis, and coccidioidomycosis; in the last of these, an evaluation is planned of amphotericin in the disseminated and meningeal forms. This drug is to be evaluated as well in histoplasmosis on a randomized basis.

Pleural Effusions

The value of thoracotomy in the diagnosis of pleural effusions was reported in a study from an Army Hospital. In 38 cases of proved tuberculosis, pleural biopsy alone revealed nonspecific fibrosis in 5, whereas the lung revealed tuberculous changes. In 18 cases,in which the tuberculin test was positive, thoracotomy gave no evidence of tuberculosis. Although these patients may have tuberculosis, they are being observed without therapy on the basis of the negative biopsy. (Rothstein, E., The Seventeenth Veterans Administration-Armed Forces Conference on the Chemotherapy of Tuberculosis: New England J. Med., 258: 1199-1204, June 12, 1958)

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